

Process Optimization of Methyl 2-Methoxy-5-Aminosulfonyl Benzoate

Wen Long XU, Cui Juan GUO, Tao LI, Si Quan LIU*

School of Chemical Engineering and Technology, University of Jinan, Jinan, Shandong 250022, China

E-mail: chm_Liusq@ujn.edu.cn

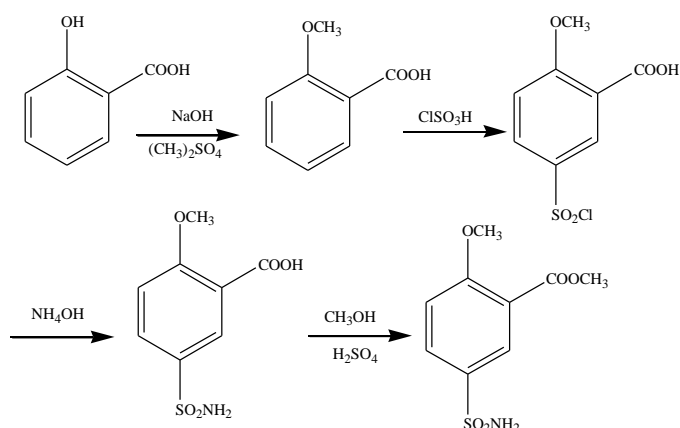
Abstract. Methyl 2-methoxy-5-aminosulfonyl benzoate as an intermediate of sulpiride was synthesized from salicylic acid as precursor, which generally consisted of four reactive steps as to etherification, sulfonyl chloride, amine and lipid. Here in, after optimization of reaction conditions such as molar ratio, reaction time and reaction temperature, the yield of the four-step reactions can be improved as to 92.6% (etherification), 95.7% (sulfonyl chloride), 75.8% (amine) and 97.4% (esterification), respectively, which resulted to the efficient improvement of total yield (63.7%). The structures and purity of all synthesized compounds was confirmed by ¹HNMR and HPLC.

1. Introduction

Methyl 2-methoxy-5-aminosulfonyl benzoate is an important intermediate for the synthesis of sulpiride [1], which is the main drug for treatment of psychiatric disorders such as schizophrenia and depression. The synthetic route of methyl 2-methoxy-5-aminosulfonyl benzoate is composed mainly of etherification (phenol hydroxyl), sulfonyl chloride, amination and esterification, which prepared successfully with the help of salicylic acid and methyl salicylate as precursor. The raw materials of the synthetic route are salicylic acid and methyl salicylate [4-10], which was synthesized by etherification (phenol hydroxyl), sulfonyl chloride, amination and esterification.

The synthetic route using methyl salicylate as starting materials possessed low yield, which can't reach to the medicinal standard. Furthermore, this synthetic route had huge "three-wastes" inevitably, which was not beneficial to industrial production. In this paper, we used salicylic acid as initial material to conduct pilot plant test based on the research achievement of lab test. Furthermore, we established an industrial production equipment at Liaocheng in Shandong province. The detail synthetic procedure is illustrated at scheme 1:





Scheme 1 the synthetic procedure of Methyl 2-Methoxy-5-Aminosulfonyl Benzoate

2. Reagents and Instruments

Salicylic acid was obtained from Jinan Huifengda Chemical Co., Ltd. Methanol was purchased from Jinan Dehou Chemical Co., Ltd. Dimethyl sulfate was from Zibo Jinkun Chemical Industry Co., Ltd. Sodium hydroxide and Sodium carbonate was obtained Zibo Lusuo Chemical Co., Ltd. Concentrated sulfuric acid, Concentrated hydrochloric acid, Zibo sulfuric acid plant; Chlorosulfonic acid and dichloromethane was purchased from Luxi chemical industry. All raw materials are not purified before use.

The melting point of the product was determined by WRS-1B digital melting point meter. The purity of the product was confirmed by W3000 high performance liquid chromatograph (DENEX, USA). ¹HNMR was carried out by Bruker ARX-400MHz nuclear magnetic resonance spectrometer using TMS as internal standard, CDCl₃ or DMSO-d₆ as solvents. Glass reactors (15 L, 50 L) was obtained from Zhengzhou ambitious experimental equipment Co., Ltd. GDSZ-2040 high and low temperature cycle device was form Zhengzhou ambitious Experimental Equipment Co., Ltd.

3. Experimental sections

3.1 Synthesis of 2-methoxybenzoic acid

0.8 kg (20 mol) sodium hydroxide was dissolved into 4.7 L of water and transferred into 15 L glass reaction kettle and keep stir. After that, the temperature of reaction kettle was decreased as to 0 °C by the treatment of low temperature cycle device. Then, 1.38 kg (10 mol) salicylic acid was added into above solution until dissolved completely. After that, 1 L (10.5 mol) dimethyl sulfate was sequentially added into above solution and keep stirring for 30 minutes at 0 °C. Next, after the freezer shut off and the reaction liquid was heated as to 35 °C for 30 minutes. Then, 1 L (10.5 mol) of dimethyl sulfate was added sequentially and heating up to 45 °C for 1.0 hour. Next, the mixed solution was heated to reflux for 2.0 hours. The pH of mixed solution was adjusted by 40% sodium hydroxide to 10, which continuously refluxed for 2.0 hours and cooled naturally to room temperature. Finally, the pH of mixed solution was adjusted to 1 by hydrochloric acid, which can generate large amounts of white precipitation after stirred for 30 minutes. The final products was washed and dried at oven to obtain 1.4 kg of 2-methoxybenzoic acid.

0.3 kg (7.5 mol) sodium hydroxide was dissolved into 3 L water and transferred into 15 L of glass reaction caldron and keep stir continuously. Next, 2-methoxybenzoic acid was added slowly until saturated. The pH of above solution was adjusted to 3-4 by a pH of 3.2 acetic acid sodium acetate buffer solution, which can generate white precipitation for stirred 1.0 hour. The final product was dried, which can obtain 1.296 kg of 2-methoxybenzoic acid and the yield and purity can reach to 92.6% and 98.60%, respectively. The 2-methoxybenzoic acid was characterized as follows: (1) Chromatographic

column ODS C18 4.6 x 250 mm (Flow phase: methanol/water 70/30; Velocity: 1.0 mL/min; detection wavelength 254 nm); (2) Melting point 101.5 - 101.7 °C (The literature value [11]: 101°C); (3) ¹HNMR (400 MHz, CDCl₃, TMS), δ:3.83(s, 3H,OCH₃), δ:6.98(d,J=2.0 Hz, 1H, PhH) δ:7.01(d,J=2.0 Hz, 1H,PhH) δ:7.18(d,J=2.0 Hz, 1H, PhH) δ:7.34(d,J=2.0 Hz, 1H,PhH), δ:12.61(s,1H, COOH).

3.2 Synthesis of 2-methoxy-5-sulfonyl chlorobenzoic acid

4 kg (34.3 mol) of chlorosulfonic acid was transferred into 15 L of glass reaction kettle and keep stir continuously. After that, the temperature of reaction kettle was decreased as to 0 °C. Then, 1.0 kg (6.6 mol) of 2-methoxybenzoic acid was added into above solution until dissolved completely. Next, after the freezer shut off, the reaction liquid was heated as to 50 °C for 1hour. And the reaction liquid was heated as to 70 °C for 2 hours and cooled to room temperature subsequently. Then, above solution was transferred into glass reaction kettle containing 50 kg of ice water and keep stir, which can obtain large amounts of white precipitate. The suspension solution was stirred for 30 minutes. The final product was filtered, washed and dried to obtain 1.576 kg 2-methoxy-5-sulfonyl-chlorobenzoic acid. The yield was reached to 95.7% and the purity was to 95.7%. The 2-methoxy-5-sulfonyl chlorobenzoic acid was characterized as follows: (1) Chromatographic column ODS C18 4.6 x 250 mm (Flow phase: methanol/water 70/30;Velocity: 1.0 mL/min; detection wavelength 254 nm); (2) Melting point 147.8-148.6 °C (literature value [12] : 147-149 °C); (3) ¹HNMR(400 MHz,CDCl₃,TMS) δ:3.82(s,3H,OCH₃), δ:7.01(d,J=2.0 Hz, 1H, PhH) δ:7.10(d,J=2.0 Hz, 1H,PhH) ,δ:7.34(s, 1H,PhH),δ: 12.61 (s,1H, COOH).

3.3 Synthesis of 2-methoxy-5-amino-sulfonyl benzoic acid

28% of the concentrated ammonia 10 L (148.4 mol) was added to 15 L glass reaction kettle in room temperature and keep stir continuously. Following added into 2 kg (9.0 mol) 2-methoxy-5-sulfonyl chlorobenzoic acid, the above solution was heated up to 30 °C for 4.0 hours. After reacted completely, the reactive solution was cooled to room temperature, which the pH was adjusted to 3 by 15% hydrochloric acid solutions. After that, the reactive solution was stirred for 30 minutes and resulted to generate large amounts of white precipitate. The final product was filtered washed and dried, which can obtain 1.398 kg of 2-methoxy-5-amino-sulfonyl benzoic acid. The yield was reached to 75.8% and the purity was as to 98.3%. The 2-methoxy-5-amino-sulfonyl benzoic acid was characterized as follows: (1) Chromatographic column ODS C18 4.6 x 250 mm (Flow phase: methanol/water 70/30;Velocity: 1.0 mL/min; detection wavelength 254 nm); (2) Melting point 220.6-221.7 °C (literature value[12]: 220 °C); (3) ¹HNMR(400 MHz,DMSO-d₆,TMS) δ:3.8(s,3H,OCH₃) δ:6.99(d,J=2.0 Hz, 1H, PhH) δ:7.12 (d,J=2.0 Hz,1H,PhH) ,δ:7.34(s, 1H,PhH), δ:8.2(d,J=2.4 Hz,2H, NH₂)δ: 12.61 (s,1H, COOH).

3.4 Synthesis of Target Product Methyl 2-methoxy-5-aminosulfonyl benzoate

6 kg (187.5 mol) methanol added to 15 L glass reaction kettle and keep stir. Then, 0.6 kg (2.94 mol) of 2-methoxy-5-amino-sulfonyl benzoic acid and 0.51 kg (5.73mol) of sulfuric acid was added into above solution. The mixed solution was heated to reflux for 6 hours. Next, the redundant methanol was removed through rotary evaporation. After that, 5.4 L 15% of sodium carbonate solution was added subsequently and keep stir for 30 minutes. Finally, the obtained white solid products was washed and dried at drying oven. 0.62 kg of Methyl 2-methoxy-5-aminosulfonyl benzoate was obtained, which can give a high yield as to 97.4% and a high purity as to 99.2%. The methyl 2-methoxy-5-aminosulfonyl benzoate was characterized as follows: (1) ODS chromatography column C18 4.6 x 250 mm (Flow phase: methanol/water 85/15; Velocity: 1.0 mL/min, detection wavelength: 254 nm); (2) Melting point 160.4 -161.3°C (literature value [13]: 159-160 °C); (3) ¹H-NMR (400 MHz, DMSO-d₆, TMS); δ: 3.8 (s, 3H, OCH₃), δ: 3.91 (s, 3H, COOCH₃), δ: 7.05 (d, J = 2.0 0 Hz, 1H, PhH) (D, J = 2.0 Hz, 1H, PhH), δ: 7.37 (s, 1H, PhH) δ: 8.1 (d, J = 2.4 Hz, 2H, NH₂).

4. Results and Discussion

4.1 Synthesis of 2-methoxybenzoic Acid

In the synthesis of 2-methoxybenzoic acid, sodium hydroxide was reacted with hydroxyl and carboxyl of salicylic acid to obtain salt, and then the above salt (phenol sodium) was sequentially reacted with sulfuric acid dimethyl ester. The results of lab test demonstrated that the best molar ratio of salicylic acid and sodium hydroxide was to 1: 2.1. Excessive sodium hydroxide would react with subsequent dimethyl sulfide, resulting to the loss of dimethyl sulfate. Hence, the above result would lead to insufficient methylation reagent, which resulted to inadequate reaction of salicylic acid to incomplete etherification reaction. When the molar ratio of salicylic acid to dimethyl sulfate was 1: 2.3, the yield was the highest. Too little dimethyl sulfate would cause incomplete reaction, whereas excessive dimethyl sulfate would cause waste obviously. What's more, the reaction time also has an important effect on the yield of the product. The experimental results show the optimized reaction time was to 5 hours. Under the optimized conditions, the yield of 2-methoxybenzoic acid can be as high as 92.6%.

4.2 Synthesis of 2-methoxy-5-sulfonyl chlorobenzoic acid

The affecting factors of the yield of 2-methoxy-5-sulfonyl chlorobenzoic acid are mainly the amount of chlorosulfonic acid, reaction temperature and reaction time. The first step is the sulfonation reaction between chlorosulfonic acid and 2-methoxybenzoic acid to produce 2-methoxy-5-sulfonate benzoic acid. The above products were reacted with chlorosulfonic acid sequentially to get the target product. The lab test showed that chlorosulfonic acid was not only as a reagent, but also as a solvent. When the acid chloride reaction is too little, the reaction is not complete result to the low yield. After optimization, the best molar ratio of methoxy benzoic acid and chlorosulfonic acid was to 1:5. Sulfonation reaction is a strong exothermic reaction, high temperature will produce polysulfonic acid-based products and low temperature will make the longer time of acid chlorination. The best reactive temperature was to 50-70 °C. The effect of reaction time was investigated subsequently. The best reaction time was to 2 hours. Although the reaction time was lengthened, the yield was not increased significantly. Under the optimized experimental conditions, the yield of 2-methoxy-5-sulfonyl chlorobenzoic acid can reach to 95.7%.

4.3 Synthesis of 2-methoxy-5-sulfamoyl benzoic Acid

In the amination reaction of 2-methoxyl-5-amino-sulfonyl benzoic acid, the main influence factors were mainly ammonia concentration, reaction temperature and reaction time. Firstly, we investigated two approaches of animation reaction: ventilation with ammonia in solvent and ammonium hydroxide as amino-reactant and solvent. In this section, the way of ventilation with ammonia in methyl alcohol and tetrahydrofuran would cause the rapid reaction, resulting to the incomplete reaction of 2-methoxy-5-sulfamoylbenzoic acid owing to the formation of 2-methoxy-5-sulfamoyl benzoic acid coated on the surface of the reaction. On the contrary, the lab test indicated that the way of ammonium hydroxide as amino-reactant and solvent can provide better experimental results. Secondly, the reactive temperature was the more important factor. The optimized amination temperature was to 30 °C. The low temperature would result to the long amination time, whereas high temperature can result to the generation of by-product owing to the hydrolysis of sulfonyl chloride. Finally, we evaluated the effect of reaction time. The optimized reaction time was to 5 hours. The extended reaction time can't cause the significant improvement of yield. As a consequence, the best reactive temperature was to 30 °C and the best mole ratio between 2-methoxy-5-sulfonylchlorobenzoic acid and ammonium hydroxide was to 1:20 and the best reactive time was to 5 hours. Under the best conditions, the yield can reach to 75.8%.

4.4 Synthesis of methyl 2-methoxy-5-aminosulfonyl benzoate

2-methoxyl-5-amino-sulfonyl benzoic acid was catalyzed by concentrated sulfuric acid through methanol esterification to obtain methyl 2-methoxy-5-aminosulfonyl benzoate. Methanol was used as

esterification reagent and solvent. The results demonstrated that too little methanol would lead to the incomplete dissolution of reactant and extended reaction time. However, superfluous methanol can result to the loss of energy. The lab test showed that the best reactive time was to 8 hours, which can ensure the complete esterification reaction. The yield of product would not improve through the approach of extended reaction time. Furthermore, we optimized the molar ratio of 2-methoxy-5-ammonia sulfonyl benzoic acid, methanol and sulfuric acid was to 1: 55: 1.1. Under the optimized experimental conditions, the yield of 2-methoxy-5-aminosulfanoyl benzoic acid methyl ester can reach to 97.4%.

4.5 Pilot Results Discussed

Table 1 Effects of Different Magnification Factors on Product Yield

Amplification factor	Salicylic acid	Dimethyl sulfate	Sodium hydroxide	Chlorosulfonic acid	Ammonia	Methyl alcohol	Sulfuric acid	yield
10	1.38	2.66	0.8	5.20	7.88	13.98	1.18	63.7
8	1.10	2.13	0.64	4.14	6.30	11.18	0.94	64.5
9	1.12	2.39	0.72	4.66	7.09	12.58	1.06	61.9
11	1.52	2.93	0.88	5.70	8.67	15.38	1.30	63.2
12	1.66	3.20	0.96	6.22	9.45	16.78	1.42	64.1

We carried out pilot plant test based on the results of lab test, shown in Table 1. Under the different magnification coefficient, the yield is not much difference, which indicated that the test results meet the production requirements.

5. Conclusion

2-methoxyl-5-amino-sulfonyl benzoate was synthesized successfully by 4 steps using salicylic acid as the starting material. The total yield was to 63.7%, which was higher than previous work. The structure and purity of the intermediate and final product was characterized by magnetic resonance hydrogen spectrum, melting point and high performance liquid chromatography. What's more, the industrial production facility of 300T/a was built successfully after the pilot amplification. The intermediate (2-methoxy-5-chlorosulfonylbenzoic acid) was synthesized by one pot using chlorosulfonic acid as sulfonation and acyl chlorination reagent, which can be avoidance of the waste of sulfoxide chloride due to the absorbance of acyl chloride process. This reaction possessed mild reaction conditions and high yield, which can reduce "three waste". Compared with the existing production technology, the new technology can solve the hydrolysis in the process of methoxy methyl benzoic acid sulfonated functionalization, which can reduce the cost of production. Furthermore, the toluene was instead by water as solvent, which was accordance of the idea of green synthesis.

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